REMARKS

Claims 1-57 of the subject application were pending. Applicants have amended claims 1-2, 8-15, 19, 21-22, 24-38, 40, 42-45, 47-48, 50-51, 53-54, and 56. Applicants are now canceling claims 3, 39, 49, 52, and 55, such cancellation intended to be without prejudice to applicants' right to again present claims of the same or a similar scope in this or a subsequently filed application. Accordingly, claims 1-2, 4-38, 40-48, 50-51, 53-54, and 56-57 are present for further examination.

In view of the amendments and the following discussion, applicants respectfully request that the Examiner reconsider and withdraw the rejections made in the outstanding Office Action.

Support for the Amendments

Applicants have amended the claims in order to more clearly describe and distinctly claim the subject matter of applicants' novel crystalline Form III of (S)-repaglinide, methods for preparing Form III, methods for preparing an amorphous form of (S)-repaglinide, and methods for preparing Form II of (S)-repaglinide.

Specifically, applicants have canceled claim 3 and incorporated the subject matter therein into independent claim 1 to recite a crystalline Form III of (S)-repaglinide "having an X-ray powder diffraction pattern substantially as shown in Figure 1."

Applicants have also incorporated the subject matter of claim 3 into independent claim 15 to recite a "pharmaceutical composition comprising: a) a compound which is a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1...".

Applicants have also incorporated the subject matter of claim 3 into independent claim 19 to recite a "process for preparing a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1...".

Applicants have also incorporated the subject matter of claim 3 into independent claim 36 to recite a "process for preparing a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1...".

Applicants have also canceled claim 39 and incorporated the subject matter therein into independent claim 38 to recite an amorphous form of (S)-repaglinide "having an X-ray powder diffraction pattern substantially as shown in Figure 4."

Applicants have also incorporated the subject matter of claim 39 into independent claim 40, and the claims dependent thereon, to recite a process for making an amorphous form of (S)-repaglinide, "having an X-ray powder diffraction pattern substantially as shown in Figure 4".

Applicants have also amended claim 50 to recite a process for preparing a crystalline Form II of (S)-repaglinide, "having an X-ray powder diffraction pattern substantially as shown in Table 3...". This amendment is supported in the specification at, for example, page 10.

Applicants have also amended claims 1-2, 8-15, 19, 21-22, 24-38, 40, 42-45, 47-48, 50-51, 53-54, and 56 to correct certain minor procedural language.

These amendments to the claims are fully supported in the specification as originally filed, and thus no new matter is introduced by these amendments in accordance with 35 U.S.C. § 132. Accordingly, applicants request entry of these amendments.

Rejection of Claims 38 and 40-49 under 35 U.S.C § 102(b) as being anticipated by *Grell et al. '924.*

The Examiner has rejected claims 38 and 40-49 under 35 U.S.C § 102(b) as being anticipated by United States Patent No. 5,312,924 (*Grell et al. '924*). The Examiner states that *Grell et al. '924* discloses a noncrystalline solid, which is amorphous and is obtained by the same process as claimed by applicants (example 4, col. 23, lines 15-17). Applicants' claims, as amended, obviate the Examiner's rejection.

As set out above, applicants have canceled claim 39 and incorporated the subject matter therein into independent claim 38. The Examiner has not rejected claim 39. Amended claim 38 now recites a "compound which is an amorphous form of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 4."

Applicants have also incorporated the subject matter of claim 39 into independent claim 40, and the claims dependent thereon. Amended claim 40 now recites a "process for making an amorphous form of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 4, said process comprising: (a) providing a solution of (S)-repaglinide in a C_1-C_4 alcohol; (b) cooling said solution so that a solid mass separates; and (c) isolating said separated solid mass to provide the amorphous form of (S)-repaglinide. Claims 41-49 are dependent from claim 40.

Grell et al. '924 discloses the use of phenylacetic acid benzylamides and (S)(+)-2-ethoxy-4-[N-{1-2-piperidino-phenyl)-3-methyl-1-butyl}-aminocarbonylmethyl]-benzoic acid, which compounds affect intermediate metabolism such as lowering blood sugar. Example 4 in *Grell et al. '924* discloses the preparation of the subject compound with the residue crystallized from petroleum ether by the addition of ethanol.

Applicants submit that *Grell et al. '924* does not anticipate applicants' claims. *Grell et al. '924* discloses crystallization of (S)-repaglinide from petroleum ether by the addition of ethanol. Applicants' amorphous form of (S)-repaglinide is prepared by providing a solution of (S)-repaglinide in a C_1-C_4 alcohol and cooling the solution to provide the amorphous form of (S)-repaglinide. *Grell et al. '924* also does not disclose an amorphous form of (S)-repaglinide having an X-ray powder diffraction pattern substantially as shown in Figure 4. In summary, *Grell et al. '924* does not teach each and every element of applicants' amorphous form of (S)-repaglinide. Accordingly, *Grell et al. '924* does not anticipate applicants' claims under 35 U.S.C. § 102(b).

Polymorphs arise when molecules of a compound arrange in the solid state in distinct ways. By varying the temperature of the solution and using different solvents, different polymorphs can be formed. Although identical in chemical composition, polymorphs can have very different properties. Polymorphs are distinguishable by various analytical techniques, especially X-ray powder diffraction patterns.

Under 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in the prior art. *Akzo N.V. v. U.S. International Trade Commission*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986), cert. denied, 482 U.S. 909 (1987). Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *W.L. Gore & Associates v. Garlock, Inc.*, 220

USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 221 USPQ 481, 485 (Fed. Cir. 1984) (emphasis added). We think the precise language of 35 U.S.C. §102 that "a person shall be entitled to a patent unless," concerning novelty and unobviousness, clearly places a burden of proof on the Patent Office which requires it to produce the factual basis for its rejection of an application under §102 and §103. *In re Warner*, 154 USPQ 173, 177 (C.C.P.A. 1967), cert. denied, 389 U.S. 1057 (1968).

Hence, the Examiner's rejection of claims 38 and 40-49 under 35 U.S.C § 102(b) as being anticipated by *Grell et al.'924* should be withdrawn.

Rejection of Claims 1 and 34-35 under 35 U.S.C §102 (b) as being anticipated by *Grell et al. '924.*

The Examiner has rejected claims 1 and 34-35 under 35 U.S.C §102(b) as being anticipated by United States Patent No. 5,312,924 (*Grell et al. '924*). The Examiner states that *Grell et al. '924* (col. 23) discloses crystallized compounds of the present claims. The Examiner argues that a novel or unobvious chemical product is identified by its chemical nature (i.e., its elemental content and their ratios) and that many pharmaceutical solids exhibit polymorphism, which is defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. The Examiner concludes that the term "Form III" does not offer any demarcation of the product from the prior art crystalline product as represented by the compound name since Form III or Form A, B, or C in the prior art are not notations known in the chemical art to represent conventional characteristics in demarcating chemical products. Applicants' claims, as amended, obviate the Examiner's rejection.

As set out above, applicants have canceled claim 3 and incorporated the subject matter therein into independent claim 1. The Examiner has not rejected claim 3. Amended claim 1 now recites a "compound which is a crystalline Form III of (S)-

repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1."

Claims 34-35 ultimately depend from claim 19. Applicants have also incorporated the subject matter of claim 3 into independent claim 19. Amended claim 19 now recites a "process for preparing a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1, said process comprising: (a) providing a solution of (S)-repaglinide in a haloalkane solvent; (b) contacting said solution with a C_5-C_{10} aliphatic or alicyclic hydrocarbon anti-solvent thereby forming a precipitate; and (c) isolating the precipitate to provide the crystalline Form III of (S)-repaglinide."

Applicants submit that *Grell et al. '924* does not anticipate applicants' claims. *Grell et al. '924* discloses crystallization of (S)-repaglinide from petroleum ether by the addition of ethanol. Applicants' crystalline Form III of (S)-repaglinide is prepared by providing a solution of (S)-repaglinide in a haloalkane solvent and contacting the solution with a C_5-C_{10} aliphatic or alicyclic hydrocarbon anti-solvent thereby forming a precipitate and providing the crystalline Form III of (S)-repaglinide. *Grell et al. '924* also does not disclose a crystalline Form III of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1. In summary, *Grell et al. '924* does not teach each and every element of applicants' crystalline Form III of (S)-repaglinide. Accordingly, *Grell et al. '924* does not anticipate applicants' claims under 35 U.S.C. § 102(b).

Hence, the Examiner's rejection of claims 1 and 34-35 under 35 U.S.C §102 (b) as being anticipated by *Grell et al. '924* should be withdrawn.

Rejection of Claims 1-37, 39, and 50-57 under 35 U.S.C. § 103(a) as being unpatentable over *Grell et al. '924* in view of *Grell et al. J. Med. Chem.* and *Brittain*.

The Examiner has rejected claims 1-37, 39, and 50-57 under 35 U.S.C. § 103(a) as being unpatentable over *Grell et al. '924* in view of J. Med. Chem. **1998**, *41*, 5219-5246 (*Grell et al. J. Med. Chem.*) and Polymorphism in Pharmaceutical Solids, edited by Harry G. Brittain, Marcel Dekker 1999 (*Brittain*). The Examiner states that *Grell et al.*

'942 discloses compounds that anticipate the base claims as pointed out above. The Examiner concedes that *Grell et al. '942* does not disclose the physical properties of the prior art products or the method of making the products employing alternative solvents. The Examiner argues that *Grell et al. J. Med. Chem.* discloses making different crystalline forms using various solvents (page 5227, paragraph below Table 2). The Examiner further argues that *Brittain* discloses that "in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or conformations of the molecules."

The Examiner states that the claims are *prima facie* obvious because the instant claims differ from the known products merely by forms and the physical properties innate to the forms. The Examiner argues that there is nothing unobvious about the innate nature of a drug because it is recognized that the innately existed different "morph" will display different physical properties such as X-ray diffraction pattern, melting point, etc. (*Brittian* at p. 178-179, 219). The Examiner contends that for a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, purification, preparation or synthesis, hydroscopicity, recovery, or prevention of precipitation. The Examiner argues that *Grell et al. J. Med. Chem.* (p. 5227) discloses using different solvents in the crystallization process. The Examiner concludes that in the absence of unexpected results, the use of such different solvents may produce products with different physical properties which are innate to the product. Applicants' claims as amended obviate the Examiner's rejection.

As set out above, applicants have amended claim 1, 19, 38, and 40.

Applicants have also amended claim 50 to recite a "crystalline Form II of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Table 3". Amended claim 50 now recites a "process for preparing a crystalline Form II of (S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Table 3, said process comprising: (a) providing a solution of (S)-repaglinide in an aromatic hydrocarbon solvent, with the proviso that said solvent does not include petroleum ether; (b) cooling said solution thereby separating a solid mass; and (c) isolating said

solid mass to provide the crystalline Form II of (S)-repaglinide." Claims 51-57 are dependent from claim 50.

The Examiner concedes that *Grell et al. 942* does not disclose the physical properties of (S)-repaglinide or the method of making the products employing alternative solvents.

The *Grell et al. J. Med. Chem.* reference discloses the structure-activity relationships of two series of hypoglycemic benzoic acid derivatives. Table 2 in *Grell et al. J. Med. Chem.* discloses the substituted benzoic acid derivatives prepared and their respective pharmacological activities. *Grell et al. J. Med. Chem.* does not disclose any polymorphs of (S)-repaglinide and does not disclose any of applicants' processes for preparing polymorphs of (S)-repaglinide

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 706.02(j)

The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp,* 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). MPEP 706.02(j).

The art recognizes the importance of identifying all possible polymorphic forms of a drug substance, and the difficulties encountered in doing so. See, for example, A. Goho, "Tricky Business," *Science News*, Vol. 166, No. 8, pages 122-123 (August 21, 2004), an eight-page website reprint being enclosed herewith for the convenience of the

Examiner. The U.S. Food and Drug Administration published a draft guidance document in December 2004 relating to polymorphism, recommending that ANDA applicants for marketing approval investigate whether their drug substance can exist in polymorphic forms, including crystalline forms, amorphous forms, and solvates.

Hence, the Examiner's rejection of claims 1-37, 39, and 50-57 under 35 U.S.C. §103(a) as being unpatentable over *Grell et al. 924* in view of *Grell et al. J. Med. Chem.* and *Brittain* should be withdrawn.

Rejection of Claims 8-18 under 35 U.S.C. §112, first paragraph.

The Examiner has rejected claims 8-18 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that it is well known in the pharmaceutical formulation field that polymorphs may undergo transformation when being formulated into compositions (*Rouhi*, Chem. Eng. News, 24 February 2003, pp. 34-35). The Examiner argues that in absence of any description or factual evidence, the specification lacks description and enablement that the pharmaceutical composition contains the claimed "form" without transformation and there is no basis in the specification to support the transformation of less than 1-5% as found in claims 9-14. Applicants respectfully traverse the Examiner's rejections.

Applicants' independent claim 8, as amended, provides a composition comprising (S)-repaglinide as a solid, wherein at least 80% by weight of said solid (S)-repaglinide is in a crystalline Form III, which has an X-ray powder diffraction pattern, expressed in terms of 2 theta angles, that includes five or more peaks selected from the group consisting of 4.44 ± 0.09, 6.81 ± 0.09, 7.80 ± 0.09, 9.28 ± 0.09, 11.09 ± 0.09, 11.89 ± 0.09, 12.92 ± 0.09, 13.46 ± 0.09, 14.34 ± 0.09, 15.77 ± 0.09, 16.24 ± 0.09, 17.08 ± 0.09, 18.06 ± 0.09, 18.75 ± 0.09, 19.25 ± 0.09, 19.59 ± 0.09, 19.99 ± 0.09, 20.34 ± 0.09, 21.18 ± 0.09, 21.96 ± 0.09, 22.18 ± 0.09, 22.58 ± 0.09, 23.24 ± 0.09, 23.77 ± 0.09, 24.08 ± 0.09, 25.02 ± 0.09, 25.31 ± 0.09, 25.78 ± 0.09, 26.67 ± 0.09, 27.39 ± 0.09, 28.03 ± 0.09, 30.26 ± 0.09, 35.50 ± 0.09, and 38.74 ± 0.09 degrees.

Applicants' independent claim 15, as amended, provides a pharmaceutical composition prepared by combining: a) a compound which is a crystalline Form III of

(S)-repaglinide, having an X-ray powder diffraction pattern substantially as shown in Figure 1; and b) a pharmaceutically acceptable carrier or diluent.

The *Rouhi* reference discloses that polymorphs may undergo transformation when being formulated into pharmaceutical compositions but *Rouhi* also discloses that polymorphism and crystallization may be mastered from start to finish (*Rouhi* at p. 34). The Examiner's position that applicants' polymorphs may undergo transformation when being formulated into compositions is only speculation.

Applicants' specification need describe the invention only in such detail as to enable a person skilled in the most relevant art to make and use it. When an invention involves distinct arts, that specification is adequate which enables the adepts of each art, those who have the best chance of being enabled, to carry out the aspect proper to their specialty.

> The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence the specification need not disclose what is well known in the art. *Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.,* 221 USPQ 481, 489 (Fed. Cir. 1984)

> It has been consistently held that the first paragraph of 35 U.S.C. §112 required nothing more than objective enablement... In satisfying the enablement requirement, as application need not teach, and preferably omits that which is well-known in the art.....How such a teaching is set forth, whether by the use of illustrative examples or by broad descriptive terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. §112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support. .
>
> The error we see in *Staehelin's* approach to the question before us is that *Staehelin* would require a patent specification to be a blueprint, which, if followed, would unfailingly reproduce exactly an applicant's claimed invention. However, the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 U.S.C. §112, first paragraph. *Staehelin v. Secher,* 24 USPQ2d 1513, 1516 (B.P.A.I. 1992)

Hence, the Examiner's rejection of claims 8-18 under 35 U.S.C. §112, first paragraph, should be withdrawn.

In view of the foregoing remarks, applicants request reconsideration pursuant to 37 C.F.R. § 112 and allowance of the claims pending in this application. Applicants suggest that the Examiner can telephone the undersigned attorney should the Examiner have any questions or comments, which might be most expeditiously handled by a telephone conference.

No fee is deemed necessary in connection with the filing of this Response. If any fee is required, however, authorization is hereby given to charge the amount of such fee to Deposit Account No. 50-3221.

Respectfully submitted,

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